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Epidemiology and the Concept of Causation in Multifactorial Diseases[1]

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Unlike infectious diseases of the past, diseases prevalent in modern industrialized societies have multifactorial origins whose complexity so far has defied an integrated scientific understanding. Their epidemiologic investigation suffers from the conceptual inability of formulating plausible causal hypotheses that mimic a complex reality, and from the practical difficulties of running elaborate studies controlled for multifactorial confounders. Until biomedical research provides a satisfactory understanding of the complex mechanistic determinants of such diseases, epidemiology can only field reductionist causal hypotheses, leading to results of uncertain significance. Consensual but rationally weak criteria devised to extract inferences of causality from such results confirm the generic inadequacy of epidemiology in this area, and are unable to provide definitive scientific support to the perceived mandate for public health action. © 1989 Academic Press, Inc.

INTRODUCTION

Because it deals with people's lives, epidemiology is an exercise of political significance, the instrument of public health policies and social intervention.

It often produces ambiguous results, and it is not surprising to find people of divergent opinions: from those who swear by the normative validity of epidemiologic data to those who paraphrase Disraeli and say that there are lies, damn lies, statistics, and eventually epidemiology.

The entire debate hinges on the criteria that epidemiologists have adopted in their definition of causation for diseases of multifactorial origin—such as cancer, cardiovascular, respiratory, and neurological disorders of aging—namely the diseases most prevalent in modern industrialized societies that have attained unprecedented levels of collective longevity.

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The debate is first about the intellectual legitimacy of certain causal inferences, and then about the ethical use of such inferences in motivating public policies.

Even the proponents of the most permissible interpretations openly recognize that this has required a broader redefinition of the lexical or traditionally accepted concepts of causality. The justifications advanced have been succinctly summarized by Rothman (1986) in his book, where he states:

> Despite philosophic injunctions concerning inductive inference, criteria have commonly been used to make such inferences. The justification offered has been that the exigencies of public health problems demand action and that despite imperfect knowledge causal inferences must be made.

This surprisingly candid statement tells that a foundation of political imperatives has taken precedence and will override logical and scientific consideration, if policy so requires. By this admission—widely recognized as real—modern epidemiology appears to have become subservient to policy in its readiness to relax its scientific standards, and thus to have earned the right to be trashed around as in any other political squabble.

For a better understanding of the situation it will be useful to analyze the components of the problem, namely the rational definitions of causation, the precedents that persuaded epidemiologists to more permissive definitions of causation, and the actual criteria for such definitions.

THE CONCEPT OF CAUSALITY

Causality is a concept acquired early in life as we interact with the physical world. Observation of causes and effects builds up a baggage of notions that allows us to navigate with a reasonable confidence by predicting the outcome of our decisions and actions.

Eventually we extend concepts of causality beyond the immediate physical world, as we progress to identify the axioms of logic and mathematics. These in turn become the foundation of rational thinking and allow processes of inference and deduction, and the linking of physical observation and rational concepts.

Philosophers have always been fascinated with the study of sensory and mental processes, but their analysis has been protracted and frustrated by persistent methaphysical preoccupations and a yearning to attain some absolute and invariant proof that somehow could hang together our whole intellectual and physical construct.

Early thinkers were obsessed with the human mind and its discovery and disdained material observations, but once empiricism was grafted on rationalism some four centuries ago, physical sciences and their technological applications developed at a prodigious rate, despite philosophical limitations raised by many famous minds.

Hume—the philosopher from Scotland—started the criticism by stating that no matter of repeated observation could establish absolute proof of causality, since the possibility of a spurious association could not be logically ruled out.

In pursuit of a solution to this problem, a long chain of thinkers led eventually to Karl Popper and his followers, and to the notion—still widely believed today—that scientific hypotheses could never be verified but could be falsified to logical satisfaction. Popper did not solve Hume's problem, but suggested that science progresses

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through deduction from hypotheses and not from the observational inductions where Hume's problem applies (Popper, 1965).

Critics of Popper point out that falsification of scientific hypotheses also requires empirical observations, and therefore is itself open to falsification in an infinite series of fruitless proofs. It looks as if Hume's problem still remains unsolved, and yet science has progressed beyond anyone's dreams.

In fact, the problem raised by Hume is a metaphysical one, and reflects—as we mentioned—a historical quest for physical parallels of the clear-cut intellectual statements that are possible in mathematics or formal logic. Unfortunately, reality is not likely to be defineable as precisely as abstract concepts either because it is intrinsically stochastic or because we do not yet possess a satisfactory understanding of the fundamental components of matter. At present, the real world seems determined by an ever changing ambiguity of mutual transformations and equivalencies between various manifestations of energy and matter.

Besides, matter as we know it on this planet has totally different properties in a black hole, in a hot star, or in galactic dust. Even the most granted observations are only temporary and local.

The spinning of the planet slowly degrades, until a gravity lock may occur with the moon or with the sun . . . chemical reactions occur only until certain circumstances are present . . . the stock market is truly unpredictable . . . and so is human history. . . .

It took Rudolph Carnap, quantum mechanics; Gauss, the theory of relativity; Einstein, and others to declare the inevitable probabilistic nature of observations, to take us out of our anthropocentric shell, and to uncouple reality from our ancient preoccupations with impossible rational absolutes. Now we accept that observations are inescapably imperfect because of the ever changing shape of reality and because of the limitations of our senses and of the instruments by which we probe the world around us. In fact, some sixty years ago Goedel—the German logician—defined the impossibility of proving universal axioms even within a purely rational system.

Once we have made philosophical peace with the inevitable imperfection of reality, everything else follows rather easily and logically. No doubt, we can only formulate hypotheses about causes and effects in the real world, but we attach more or less credibility—and therefore utility—to these hypotheses depending on the likelihood we can assign to their outcome or veracity. The reliable frequency of an observation, such as the sun rising in the morning, is motive of reassurance, despite the long-term certainty of failure.

In other terms we speak of the probability of being right in our space/time context, which—given our awareness of imperfection—often ranges from less than one to more than zero.

Yet, despite the general uncertainty, science, its utilitarian applications, and the semantics of daily language and human behavior recognize a discontinuous nature of decision making. When existential choices are made they are at least dichotomous—as exemplified by yes–no, here-and-not-there dilemmas—and lead to nonambiguous decisions devoid of uncertainty.

The business of life demands a decisive classification of causal statements. In common language, causes that are sufficient to produce a given outcome are accorded the highest reliability, as in the case of the rotation of the earth being the cause of day

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and night. These are causes invariably followed by a given outcome, at least within the relativity of human experience.

Next in the graduatory of reliability are causes that appear not always sufficient to produce a set outcome, but that are necessarily present for the outcome to happen. These are necessary but not always successful causes, such as agents of infectious diseases.

Consistent observation of outcomes, or end results, is usually sufficient for a rationally acceptable identification of necessary and sufficient causes. However—as it is probably the case for cancer—certain outcomes may have several independent causes which could not individually appear as necessary or sufficient. In such cases only definitive mechanistic evidence—namely process evidence as opposed to end results alone—can eventually satisfy the rational identification of those causes that can be properly called facultative. It is true that mechanistic dissection would eventually reclassify facultative causes as either necessary or sufficient once specific causal links are identified at some minute detail. Yet the distinction of facultative causes is intuitively useful in the macroscopic domain of everyday observation. These classes of causes—sufficient, necessary and facultative—pretty much cover the entire meaning of causality that common people and scientists alike permit themselves to consider in arriving at definitive statements and actions.

A further semantic clarification defines the concept of proximate cause. Although an essential element, the sun is not the proximate cause of day and night, nor is the lung the cause of lung cancer. Proximate causes are identified in relation to their role in decision making, and are usually the element or elements of a situation that can be modulated, that vary or can be varied.

In the moment of starting a car everything else is invariant—motor, battery, wiring, starter, gas—except for the immediate closing of the starter and ignition circuits. Paralytic polio is the proximate effect of infection with a virulent strain of poliovirus. Nor do proximate causes have to be single events: clearly one or more covariates can be the simultaneous or sequential decisive elements of an outcome.

With these additional clarifications, people and scientists alike feel securely justified in accepting causal contexts that allow mutually exclusive decisions, with a meaning of pragmatic precision that ignores negligible residuals of uncertainty.

Such contexts are available only when sufficient or necessary or proven facultative causes can be identified. Beyond these there is another category of events that can be associated with a given outcome, but that appear neither sufficient nor necessary for its occurrence. In rational thinking and decision making, the elements of this category are not accorded definitive causal credibility. Examples are the association of lightning and rain, stock prices and shape of market trend functions, use of nylon stockings and birth rates, and so on. At their best they are utilized in constructing provisional research hypotheses, in relation to the strength of their associations. At their worst they are represented as true causes, at the service of manipulative interests.

Clearly, in the absence of logical constraints the elements of this category are open to many interpretations and, notwithstanding their continuous uses, are largely considered as chancy predictors. In fact the common language defines this third category as opinions, hints, guesses, feelings and emotions, testifying to the general perplexity about their usefulness. They cannot lead to clear-cut statements of practical certainty and causality, but can fuel much inconclusive debate.

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EPIDEMIOLOGY AND CAUSATION

Early in this century, the need and the newly discovered opportunities to control infectious diseases gave impetus to modern epidemiology. The beginnings were very promising, and the epidemiology of infectious diseases very rewarding.

By comparison to multifactorial complications, infectious diseases are relatively simple because they have well defined causes, rarely sufficient but always necessary. Inferences of causality can be made in a logic framework that no rational person could fault, and to a level of detail that includes persuasive mechanistic observations. Causes so identified can be controlled, with the pleasing result of eliminating diseases, thus reinforcing confidence in the identification of causality.

Successes with infectious diseases enhanced the credibility of epidemiologists in the eyes of the public and policy makers alike, who then expected a similar performance for chronic multifactorial diseases.

When epidemiologists turned to chronic diseases soon after World War II, they had an image and a reputation to defend. The public, reassured by successes such as the Salk vaccine, had come to think that medicine could cure anything given money and will, and euphoric legislatures allowed public health agencies to fund unprecedented efforts in the identification of the causes of chronic diseases toward their eventual control.

Today we have made impressive gains toward the elucidation of pathogenesis in cancer, cardiovascular, and respiratory chronic diseases, but no one has yet claimed to have solved their proximate causal operants or their prime biological mechanics, nor have we learned how to control or prevent them to any significant extent, few admirable exceptions notwithstanding.

The reasons for this impasse are many. First, such diseases have strong physiologic or organic components linked to the inevitable deteriorations of aging. Second, the insults which can induce, favor, or precipitate the onset of clinical disease are many and independent, and likely to operate through a variety of biologic pathways (Hiatt *et al.*, 1977).

Thus we speak of multifactorial diseases, which means two things: there are probably multiple causal components in a causative chain of events, and there are probably many causative chains of events, each with a different cluster of causal components, all leading to similar diseases.

Is there a hope of identifying definitive causes—sufficient, necessary or facultative—in a situation like this? The answer is that we are more likely to find facultative causes, but not through epidemiologic investigations that study multifactorial diseases in a generic, end-result, black-box approach, without benefit of reliable mechanistic information. With these limitations epidemiology can be expected at best to identify factors associated with a given disease, but whose causality remains hypothetical. In the future, biomedical research may discover classes of prime molecular mechanisms that trigger a disease, and the factors necessary to its progression. This could then identify the pathogenic potential of various external insults after additional insight on their internal transformations, and thus allow epidemiology to determine how decisive or partial is their causal contribution to disease.

Until then, epidemiology can have only a very modest role, and yet epidemiologists are the only ones that have spoken with certainty about causes of cancer, cardiovascu-

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lar, and other chronic diseases. Curiously, these claims have yet to land a Nobel prize. In fact, by any rational analysis, what epidemiologists have identified are epiphenomena, hints, and clues derived from associations and elevated to the status of causes by premature enthusiasm or by expedients of policy, as Rothman and others readily admit.

Various terminologies—besides causes—have been used in epidemiology for these items, such as risk factors, contributing factors, cofactors etc. However these definitions are presented with an implication of causality that rationally and factually is not warranted. The term "causoids" would be more clearly descriptive of their uncertainty, and may find wide acceptance.

What are the criteria used by epidemiologists to extract causal meaning from causoids, and how imperfect is the resulting knowledge?

Not surprising, the criteria originated with the Surgeon General's report on the effects of smoking in 1954, and were later formalized by Hill (1965) and elaborated by Rothman (1986), Susser (1986) and others.

The first criterion refers to the strength of the association, as can be numerically defined to include dose–response gradients, but a number of however strong but spurious associations can be identified in most instances.

The second is the consistency of the association in different studies, but consistent bias would produce consistently biased results. The third is specificity of a cause resulting in a single effect, but this is an unlikely happening for multifactorial diseases.

The fourth, temporal sequence—means that a cause must precede the effect, and is obviously a prerequisite but not a guarantee of causation. The fifth, coherence, refers to biological plausibility, but it is a difficult item in the absence of acceptable mechanistic understanding of the diseases involved. Coherence with a mechanistic hypothesis is not persuasive of causality until the hypothesis is clarified.

Sixth is experimental evidence, but as we have seen before, this either is not yet available or not applicable to chronic diseases of man. Susser had the very good sense of adding predictive performance as perhaps the most important criterion, and obviously a very persuasive one if verified (Susser, 1986). However, attempts at verification have spectacularly failed with multifactorial diseases (Werko, 1987). Other criteria such as plausibility and analogy are intuitively much weaker arguments.

A most interesting revelation of modern epidemiology is the recurring authoritarian proposition—by leading epidemiologists and public health officials—that if the above criteria are accepted as canons, this will generate consensus, and that consensus certifies causality. It is difficult to think of a proposition less compatible with science.

To their credit, Hill, Rothman, and others all admit that there are no reliable criteria for determining the causality of an association. Yet they all emphasize the duty of epidemiologists to make causal pronouncements in the service of public health, despite inadequate knowledge.

How imperfect are the causal claims advanced today for chronic diseases?

Several critics have classified numerous sources of methodological bias. Systematic bias and random bias, standardization, diagnostic and classification bias, exposure assessment bias, case-control versus cohort studies, questionnaire bias, data processing bias, publication bias, to mention a few (Feinstein, 1988).

However, the least understood and most insidious sources of error are the inherent

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difficulties in identifying reliable control groups in epidemiologic studies (Feinstein, 1988), and the academic propensity of most scientists—epidemiologists included—to make things easier and more manageable by formulating simple experimental hypotheses, regardless of the recognizable complexity of the corresponding reality.

It should be clear that the epidemiology of multifactorial diseases is bound to be naive and doubtful until we formulate realistically complex hypotheses and test all competing hypotheses, or at least those that appear more plausible.

For instance, today it is evident that natural carcinogenic agents are ubiquitous in the environment, more numerous and significant than man made entities.

Substantial amounts of carcinogens are produced continuously inside our bodies as byproducts of our own metabolism of by our intestinal bacteria (Ames *et al.*, 1987; Tannenbaum, 1980; IARC, 1978). Significant amounts of natural radioactive isotopes are found in our bodies. Our environment and food are naturally radioactive, and contain significant amounts of substances that are carcinogenic in animals (Ames *et al.*, 1987; NCRPM, 1987).

We truly live—and man has always lived—in a sea of carcinogens. That most of us endure to ripe old age testifies to the efficient natural defense mechanisms that evolution has introduced in our systems.

Global estimates suggest that most cancers are associated with dietary and other lifestyle factors and natural radiation, with only 1–4% being possibly associated with exposures to man made situations (Wynder *et al.*, 1977; Doll *et al.*, 1981; OTA, 1981). At the same time these and other studies indicate that most foods and many drugs and chemicals that are suspected of causing disease are also known and essential elements of life processes, and ultimately of disease prevention and of survival.

Thus it is not surprising that besides saying that food is probably the most important source of cancer determinants, it has been so far nearly impossible to sort out specific causal elements in the diet with any objective satisfaction. When we attempt to do so, seemingly insurmountable contradictions and competing hypotheses become apparent.

The association of smoking and certain cardiovascular diseases can be equally attributed to a causative role of smoking, or to a propensity to smoke in people with an independent susceptibility to cardiovascular diseases. This second hypothesis becomes even more interesting when considering the well known cardiotonic properties of nicotine, and the consistent failure to reduce mortality of the many and massive smoking-reduction experiments conducted around the world in the last decades (Werko, 1987). Yet no one has seriously tested this competing hypothesis.

What causes lung cancer? The EPA assures that natural radon exposure accounts for as much as 25,000 cases a year in the United States. OSHA on the other hand asserts, on the basis of epidemiologic studies, that as many as 50,000 cases a year are related to asbestos exposure.

A few years ago, a panel of senior epidemiologists and scientists from the NCI and other agencies issued a statement to the effect that as much as 40% of lung cancer was related to occupational exposures. The Surgeon General keeps telling that the epidemiologic evidence indicates that 90% or upwards of 100,000 cases of lung cancer a year are caused by cigarette smoking.

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While sophisticated scientists understand the politically motivated exaggeration of these claims, a common sense observer can only figure out that there are not enough lung cancer cases a year in the United States to account for all these competing claims, and is understandably puzzled. But epidemiologists assure us that the many causes of a disease can well account for more than 100% of the incidence. Rothman (1986) again in his book writes:

> There is in fact no upper limit to the sum . . . being constructed; the total of the proportion of disease attributable to various causes is not 100 percent but infinity.

Theoretically this statement could be forgiven—Rothman tells—when all the so-called causes of lung cancer were in fact necessary parts of each possible set of distinct causative chains, but the contrary is evident. Observation shows that people develop lung cancer even in the absence of one or many of the putative causal factors identified.

Do epidemiologists mean that we could prevent more than 100% of any given disease—an obviously absurd statement—or are they airing their anguish about the irreconciliable uncertainties that plague their conclusions?

Epidemiologists should admit—to themselves at least—a continuing methodological and conceptual inability to integrate the complexities of causation of most modern chronic diseases, and a poignant propensity to reductionist studies.

One conclusion seems plausible, however. Namely that while yet unknown multifactorial complications prevent telling the causal meaning of a positive association, negative findings allow for a greater confidence that the exposure under study is not an invariably causal operant, or at least not a significant one. If it were, no negative results could be expected.

To say that negative studies do not rule out a possible causality is a metaphysical argument that could not be proved or disproved in factual terms. Pragmatically it is a bankrupt argument of no concern in decision making. If well conducted epidemiologic studies of open samples of the population fail to detect risk at certain real-life exposure levels, it is convincing enough evidence for all practical purposes. Failure to accept it as such would turn the clock back to those dark ages when inane arguments and irrational fears wasted individual lives and the better energies of mankind.

At best today epidemiology can speak of putative risk factors or—as proposed—of causoids of most chronic diseases. Even in occupational studies, where the overall variables may be considerably fewer, inferences of causality may appear stronger but in fact remain hypothetical, except in those situations where removal of the presumed cause has eliminated the disease. At the opposite end of the reliability spectrum are the vague associations that occasionally emerge from the statistical sifting or dredging of generic data-bases. Here not science, but suspicions that appear more or less urgent are the true motivators of value judgments and public and private decisions.

While it can be argued what legitimate roles causoids should have in public health, it is undeniable that in fact they are official determinants of public policies, and more so to the extent that they conform with the criteria of presumed causality described above.

Public health officials and regulators usually claim statutory imperatives in using imperfect epidemiologic evidence, based on two presumptions. One—openly stated—that no other information is available, the other—usually only implied—

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that the public has nothing to lose and perhaps something to gain from the decisions taken (OTA, 1981; OSTP, 1985).

With the former it is transparent that poor information may condone, but not endorse action. The latter would be tenable if we had a reliable understanding of the network of multifactorial determinants of modern health and disease, but this we have not. Furthermore we cannot ignore that numerous experiments involving hundreds of thousand of subjects in the US and Europe have consistently failed to reduce mortality in those groups where lifestyles had been forcibly modified to reduce cancer, cardiovascular and other multifactorial diseases. Changes included a number of conditions regarding diet, smoking, blood pressure and alcohol intake, that were presumed "healthier" based on provisional epidemiologic inferences (Werko, 1987; MRFIT, 1982; Stallones, 1983; Rose *et al.*, 1983). Likewise, in many countries CVDs have posted dramatic declines since the 1950's, despite substantial increases in smoking habits, dietary fat and alcohol consumption (Nicolosi *et al.*, 1988, Ueshima *et al.*, 1987).

There is also continuous talk of the economic advantages of prevention in regard to medical costs and personal productivity, but very little is said of the studies which have addressed the intuitive notions that extending longevity will offset by many fold the immediate savings, and that planning is necessary for the escalation of later survival costs and dependency ratios.

It should be clear that most contemporary public health policies of intervention and advice in chronic multifactorial diseases rest on a foundation of causal evidence that is seldom solid, and more often rationally and factually tenuous and simplistic. They are driven by advocacy, by obligated activism, and at best by hope. Because of our persistent frustration with the scientific understanding and control of these ominous diseases, we have persuaded ourselves to relax our standards of evidence so that we could indulge in the comforting thought of doing something with a parvence of plausibility. We could be lucky, but we could also muddle through fruitless and static policies that impede a broader exploration of epidemiologic reality. We could also do serious harm.

The bold use of causoids—hints and clues—is a daily activity in the business arena, where the high risk of failure is an accepted element of the game. But is it ethical to adopt a similar game, virtually with identical rules of chance, when dealing with people's lives?

Hopefully all this is useful and may extend longevity, and public health efforts are well intended, but as a minimum we should ask in each instance whether we can forecast its outcome with reasonable certainty—how sure are we of having considered the complex big picture, have we gone beyond some superficial minimalistic assumptions, have we given a chance to equally plausible competing hypotheses, and are we reasonably sure that our policies conceal no harm.

Ultimately these questions are resolved in a political context, but as epidemiologists we have a duty to see that policy makers are not acting under illusions of scientific endorsement, and that such questions are in fact addressed. Reminders of this kind might cause the loss of some financial support, but what is the alternative to integrity? We have a responsibility to our discipline, to science, to future epidemiologists and to mankind. Today this seems to require some honest profession of modesty. After all no one could deny that we still have a lot to be modest about.

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REFERENCES

AMES, B. N., MAGAW, R., AND GOLD, L. S. (1987). Ranking possible carcinogenic hazards. *Science,* **236,** 271–275.

DOLL, R., AND PETO, R. (1981). Causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *JNCI* **66,** 1191–1308.

FEINSTEIN, A. R. (1988). Scientific standards in epidemiologic studies of the menace of daily life. *Science* **242,** 1257–1263.

GORI, G. B., AND RICHTER, B. J. (1978). Macroeconomics of disease prevention in the United States. *Science* **200,** 1124–1130.

HIATT, H. H., WATSON, J. D., AND WINSTEN, J. A., (Eds.) (1977). *Origins of Human Cancer.* Cold Spring Harbor Laboratory. Cold Spring Harbor, New York.

HILL, A. B. (1965). The environment and disease: Association or causation? *Proc. R. Soc. Med.* **58,** 295–300.

IARC (1978). *Some N-Nitroso Compounds. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.* Vol. 17, p. 36. International Agency for Research on Cancer. Lyon.

MRFIT Research Group (1982). Multiple risk factor intervention trial—Risk factor changes and mortality results. *JAMA* **248,** 1465–1477.

National Council on Radiation Protection and Measurements (NCRPM) (1987). *Exposure of the Population in the United States and Canada from Natural Background Radiation.* Report No. 94. Bethesda, MD.

NICOLOSI, A., CASATI, S., TAIOLI, E., AND POLLI, E. (1988). Death from cardiovascular disease in Italy, 1972–1981: decline in mortality and possible causes. *Int. J. Epidemiol.* **17,** 766–772.

Office of Science and Technology Policy. (OSTP) (1985). Chemical carcinogens: a review of the science and its associated principles. *Fed. Regist.* **50,** 10371–10442.

Office of Technology Assessment (OTA) (1981). *Assessment of Technologies for determining cancer risks from the environment.* U.S. Congress, Washington, DC.

POPPER, K. R. (1965). *The Logic of Scientific Research.* Harper & Row, New York.

ROSE, G., TUNSDALL-PEDOE, J. D., AND HELLER, R. F. (1983). UK heart disease prevention project: Incidence and mortality results. *Lancet* **1,** 1062–1065.

ROTHMAN, K. J. (1986). *Modern Epidemiology.* Little, Brown, Boston/Toronto.

STALLONES, R. A. (1983). Mortality and the Multiple Risk Factor Intervention Trial. *Amer. J. Epidemiol.* **117,** 647–650.

SUSSER, M. (1986). The logic of Sir Karl Popper and the practice of epidemiology. *Amer. J. Epidemiol.* **124,** 711–718.

TANNENBAUM, S. R. (1980). Ins and outs of nitrites. *Sciences,* January, p. 7.

UESHIMA, H., TATARA, K., AND ASAKURA, S. (1987). Declining mortality for ischemic heart disease and changes in coronary risk factors in Japan, 1956–1980. *Am. J. Epidemiol.* **125,** 62–72.

WERKO, L. (1987). The enigma of coronary heart disease and its prevention. *Acta Med. Scand.* **221,** 323–333.

WYNDER, E. L., AND GORI, G. B. (1977). Contribution of the environment to cancer incidence: an epidemiologic exercise. *JNCI* **58,** 825–832.

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